Case 4
Primary Hypokalemic Periodic Paralysis

Jimmy Jaworski is a 16-year-old sprinter on the high school track team. Recently, after he completed his events, he felt extremely weak, and his legs became "like rubber." Eating, especially carbohydrates, made him feel worse. After the most recent meet, he was unable to walk and had to be carried from the track on a stretcher. His parents were very alarmed and made an appointment for Jimmy to be evaluated by his pediatrician. As part of the workup, the pediatrician measured Jimmy's serum K⁺ concentration, which was normal (4.5 mEq/L). However, because the pediatrician suspected a connection with K⁺, the measurement was repeated immediately after a strenuous exercise treadmill test. After the treadmill test, Jimmy's serum K⁺ was alarmingly low (2.2 mEq/L). Jimmy was diagnosed as having an inherited disorder called primary hypokalemic periodic paralysis and subsequently was treated with K⁺ supplementation.

Q QUESTIONS

1. What is the normal distribution of K⁺ between intracellular fluid and extracellular fluid? Where is most of the K⁺ located?

2. What major factors can alter the distribution of K⁺ between intracellular fluid and extracellular fluid?

3. What is the relationship between the serum K⁺ concentration and the resting membrane potential of excitable cells (e.g., nerve, skeletal muscle)?

4. How does a decrease in serum K⁺ concentration alter the resting membrane potential of skeletal muscle?

5. Propose a mechanism whereby a decrease in the serum K⁺ concentration could lead to skeletal muscle weakness.

6. Why did Jimmy's weakness occur after exercise? Why did eating carbohydrates exacerbate (worsen) the weakness?

7. How would K⁺ supplementation be expected to improve Jimmy's condition?

8. Another inherited disorder, called primary hyperkalemic periodic paralysis, involves an initial period of spontaneous muscle contractions (spasms), followed by prolonged muscle weakness. Using your knowledge of the ionic basis for the skeletal muscle action potential, propose a mechanism whereby an increase in the serum K⁺ concentration could lead to spontaneous contractions followed by prolonged weakness.
1. Most of the body’s K⁺ is located in the intracellular fluid; K⁺ is the major intracellular cation. The intracellular concentration of K⁺ is more than 20 times that of extracellular K⁺. This asymmetrical distribution of K⁺ is maintained by the Na⁺-K⁺ adenosine triphosphatase (ATPase) that is present in all cell membranes. The Na⁺-K⁺ ATPase, using ATP as its energy source, actively transports K⁺ from extracellular fluid to intracellular fluid against an electrochemical gradient, thus maintaining the high intracellular K⁺ concentration.

2. Several factors, including hormones and drugs, can alter the distribution of K⁺ between intracellular fluid and extracellular fluid (Figure 1–7). Such a redistribution is called a K⁺ shift to signify that K⁺ has shifted from extracellular fluid to intracellular fluid or from intracellular fluid to extracellular fluid. Because the normal concentration of K⁺ in the extracellular fluid is low, K⁺ shifts can cause profound changes in the concentration of K⁺ in the extracellular fluid or in the serum.

![Figure 1-7 Internal K⁺ balance. ICF, intracellular fluid; ECF, extracellular fluid.](image)

The major factors that cause K⁺ to shift into cells (from extracellular fluid to intracellular fluid) are insulin, β-adrenergic agonists (e.g., epinephrine, norepinephrine), and alkalemia. The major factors that cause K⁺ to shift out of cells (from intracellular fluid to extracellular fluid) are lack of insulin, β-adrenergic antagonists, exercise, hyperosmolarity, cell lysis, and acidemia. Therefore, insulin and β-adrenergic agonists cause K⁺ to shift from extracellular fluid to intracellular fluid and may cause a decrease in serum K⁺ concentration (hypokalemia). Conversely, lack of insulin, β-adrenergic antagonists, exercise, hyperosmolarity, or cell lysis cause K⁺ to shift from intracellular fluid to extracellular fluid and may cause an increase in serum K⁺ concentration (hyperkalemia).

3. At rest (i.e., between action potentials), nerve and skeletal muscle membranes have a high permeability or conductance to K⁺. There is also a large concentration gradient for K⁺ across cell membranes created by the Na⁺-K⁺ ATPase (i.e., high K⁺ concentration in intracellular fluid and low K⁺ concentration in extracellular fluid). The large chemical driving force, coupled with the high conductance to K⁺ causes K⁺ to diffuse from intracellular fluid to extracellular fluid. As discussed in Case 3, this process generates an inside-negative potential difference, or K⁺ diffusion potential, which is the basis for the resting membrane potential. The resting membrane potential approaches the K⁺ equilibrium potential (calculated with the Nernst equation for a given K⁺ concentration gradient) because the resting K⁺ conductance is very high.
Changes in the serum (extracellular fluid) $K^+$ concentration alter the $K^+$ equilibrium potential, and consequently, the resting membrane potential. The lower the serum $K^+$ concentration, the greater the $K^+$ concentration gradient across the membrane, and the more negative (hyperpolarized) the $K^+$ equilibrium potential. The more negative the $K^+$ equilibrium potential, the more negative the resting membrane potential. Conversely, the higher the serum $K^+$ concentration, the smaller the $K^+$ concentration gradient, and the less negative the $K^+$ equilibrium potential and the resting membrane potential.

4. Essentially, this question has been answered: as the concentration of $K^+$ in the serum decreases, the resting membrane potential of skeletal muscle becomes more negative (hyperpolarized). Thus, the lower the serum $K^+$ concentration, the larger the $K^+$ concentration gradient across the cell membrane, and the larger and more negative the $K^+$ equilibrium potential. Because the $K^+$ conductance of skeletal muscle is very high at rest, the membrane potential is driven toward this more negative $K^+$ equilibrium potential.

5. To answer this question about why Jimmy was weak, it is necessary to understand the events that are responsible for action potentials in skeletal muscle. Figure 1–8 shows a single action potential superimposed by the relative conductances to $K^+$ and $Na^+$. The action potential in skeletal muscle is a very rapid event (lasting approximately 1 msec) and is composed of depolarization (the upstroke) followed by repolarization. The resting membrane potential is approximately $-70 \text{ mV}$ (cell negative). Because of the high conductance to $K^+$, the resting membrane potential approaches the $K^+$ equilibrium potential, as described earlier. At rest, the conductance to $Na^+$ is low; therefore, the resting membrane potential is far from the $Na^+$ equilibrium potential. The action potential is initiated when inward current (positive charge entering the muscle cell) depolarizes the muscle cell membrane. This inward current is usually
the result of current spread from action potentials at neighboring sites. If the muscle membrane is depolarized to the threshold potential (to approximately –60 mV), activation gates on voltage-gated Na⁺ channels rapidly open. As a result, the Na⁺ conductance increases and becomes even higher than the K⁺ conductance. This rapid increase in Na⁺ conductance produces an inward Na⁺ current that further depolarizes the membrane potential toward the Na⁺ equilibrium potential, which constitutes the upstroke of the action potential. The upstroke is followed by repolarization to the resting membrane potential. Repolarization is caused by two slower events: closure of inactivation gates on the Na⁺ channels (leading to closure of the Na⁺ channels and decreased Na⁺ conductance) and increased K⁺ conductance, which drives the membrane potential back toward the K⁺ equilibrium potential.

Now, we can use these concepts and answer the question of why Jimmy's decreased serum K⁺ concentration led to his skeletal muscle weakness. Decreased serum K⁺ concentration increased the negativity of both the K⁺ equilibrium potential and the resting membrane potential, as already discussed. Because the resting membrane potential was further from the threshold potential, more inward current was required to depolarize the membrane to threshold to initiate the upstroke of the action potential. In other words, firing action potentials became more difficult. Without action potentials, Jimmy's skeletal muscle could not contract, and as a result, his muscles felt weak and "rubbery."

6. We can speculate about why Jimmy's periodic paralysis occurred after extreme exercise, and why it was exacerbated by eating carbohydrates. By mechanisms that are not completely understood, exercise causes K⁺ to shift from intracellular fluid to extracellular fluid. It may also lead to a transient local increase in the K⁺ concentration of extracellular fluid. (Incidentally, this local increase in K⁺ concentration is one of the factors that causes an increase in muscle blood flow during exercise). Normally, after exercise, K⁺ is reaccumulated in skeletal muscle cells. Because of his inherited disorder, in Jimmy, this reaccumulation of K⁺ was exaggerated and led to hypokalemia. Ingestion of carbohydrates exacerbated his muscle weakness because glucose stimulates insulin secretion. Insulin is a major factor that causes uptake of K⁺ into cells. This insulin-dependent K⁺ uptake augmented the postexercise K⁺ uptake and caused further hypokalemia.

7. K⁺ supplementation provided more K⁺ to the extracellular fluid, which offset the exaggerated uptake of K⁺ into muscle cells that occurred after exercise. Once the pediatrician understood the physiologic basis for Jimmy's problem (too much K⁺ shifting into cells after exercise), sufficient K⁺ could be supplemented to prevent the serum K⁺ from decreasing.

8. Another disorder, primary hyperkalemic periodic paralysis, also leads to skeletal muscle weakness. However, in this disorder, the weakness is preceded by muscle spasms. This pattern is also explained by events of the muscle action potential.

The initial muscle spasms (hyperactivity) can be understood from our earlier discussion. When the serum K⁺ concentration increases (hyperkalemia), the K⁺ equilibrium potential and the resting membrane potential become less negative (depolarized). The resting membrane potential is moved closer to threshold potential and, as a result, less inward current is required to initiate the upstroke of the action potential.

It is more difficult to understand why the initial phase of muscle hyperactivity is followed by prolonged weakness. If the muscle membrane potential is closer to threshold, won't it continue to fire away? Actually, no. The explanation lies in the behavior of the two sets of gates on the Na⁺ channels. Activation gates on Na⁺ channels open in response to depolarization; these gates are responsible for the upstroke of the action potential. However, inactivation gates on the Na⁺ channel close in response to depolarization, albeit more slowly than the activation gates open. Therefore, in response to prolonged depolarization (as in hyperkalemia), the inactivation gates close and remain closed. When the inactivation gates are closed, the Na⁺ channels are closed, regardless of the position of the activation gates. For the upstroke of the action potential to occur, both sets of gates on the Na⁺ channels must be open; if the inactivation gates are closed, no action potentials can occur.
Key topics
Action potential
Activation gates
β-Adrenergic agonists (epinephrine, norepinephrine)
Depolarization
Exercise
Hyperpolarization
Inactivation gates
Insulin
Inward current
K⁺ distribution
K⁺ equilibrium potential
K⁺ shifts
Na⁺ channels
Outward current
Repolarization
Resting membrane potential
Threshold potential
Upstroke